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A Neutrophil's Perspective: the Innate Response to Tuberculosis Infection and the Induction of Adaptive Immunity

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Abstract

Neutrophils were traditionally viewed as short lived, terminal, innate effector cells that eliminate microbes and remove cellular debris at the site of infection or inflammation. They mediate this by phagocytosis, the release of reactive oxygen species, antimicrobial proteins and proteolytic enzymes. During recent years, studies have demonstrated that they are longer lived than initially thought and they mediate a large number of immune functions by the release of a variety of preformed and newly synthesized molecules such as cytokines and chemokines. In this review we will reconsider the mechanism by which neutrophils operate, especially focusing on the response to tuberculosis infection and we will look at a recent study indicating neutrophils as sophisticated mediators of innate and adaptive immune responses.

Keywords: Neutrophils; Activation; Neutrophil extracellular trap; Apoptosis

Introduction

Immunity is defined as a host's defence mechanism against disease. The significance of the immune system for health is gravely illustrated by the frequent observation of disease and infection in individuals with inadequate or faulty immune responses. The host's mechanism of defence consists of innate immunity, present in all healthy individuals as the first line of defence against infections; and adaptive immunity, which develops more gradually and provides specific and more specialized defence against pathogens. The importance of the immune system for host protection against infection was intensely highlighted during the advent of AIDS (acquired immunodeficiency syndrome) during the 1980's. AIDS is a spectrum disease caused by an infection with HIV (human immunodeficiency virus) [1]. As the disease progresses, the immune system steadily declines, resulting in an increased susceptibility to opportunistic infections that can become life threatening; the reactivation of latent infections such as tuberculosis; and greater incidence of several cancers. In individuals with a healthy immune system, latent tuberculosis are not eradicated but are constrained by intact immune responses. Tuberculosis is caused by infection of *Mycobacterium tuberculosis* (M. tb), an intracellular bacterium [2]. According to the World Health Organization during 2013 tuberculosis accounted for about 1.3 million deaths on average [3]. Today, one of the most prominent threats in the abolishment of the tuberculosis epidemic is multidrug resistant M. tb (MDR-TB), which developed due to extensive and uncontrolled use of antibiotics. It is evident from these statistics that more effective tuberculosis treatments and diagnostic tools are required.

Neutrophils, being the specialized front-line fighters, arrive at the scene within minutes after a breach of immunity. They are directly associated with inflammation and react vigorously against pathogenic infection, often leaving behind a trail of immunopathology. Neutrophils instruct monocytes, dendritic cells and other lymphocytes and aid as a direct connection between innate and humoral immune responses. In this review we reassess the duty of the innate immune system, especially focusing on the role neutrophils play during tuberculosis infection. We will also consider a pioneering study led by Andrea Cerutti et al. [4] in uncovering novel communications between different divisions of the immune system.

The phenotype and origin of neutrophils

Neutrophils are effector cells that form part of the innate immune system. They are also known as polymorphonuclear neutrophils (PMN's) due to their lobe shaped nuclei. Together with eosinophils and basophils they form part of the granulocyte

cell family. The cytoplasmic granules contained within neutrophils are characterized by their ability to not take on basophilic (blue) or acidophilic (red) dye stains, they instead colour pale pink during blood smear stains [4]. These native myeloid cells are formed in the bone marrow where growth factors and cytokines instruct pluripotent hematopoietic cells to differentiate into myeloblasts. These myeloblasts are mouldable cell types dedicated to develop into granulocytes. During neutrophil development, protein-containing cytoplasmic granules are formed and released into circulation following their maturation [4]. The strictly monitored process by which matured neutrophils are released from the bone marrow are regulated by cytokines and chemokines. Stimulation to release neutrophils into circulation (from the bone marrow) is governed by the SDF-1 α/CXCR4 chemokine axis, which also maintains an assemblage of neutrophils to promote rapid release should an infection arise [5]. Between 50-70% of the white blood cell population is represented by neutrophils, making them the most abundant white blood cell type. They are highly mobile and found dispersed in tissues, but are predominantly found in areas of acute inflammation and severe necrosis.

The neutrophil mode of action

Neutrophils are the first line of defence against infection and migrate to the site of inflammation or tissue damage within minutes following trauma. These innate immune cells are the first to be activated and a key attribute of acute inflammation [6]. Neutrophils undergo a process of degranulation following activation and release into circulation. During this process an extensive amount of membrane delineated granules release their payload consisting of potent anti-microbial agents, such as alkaline phosphatase- containing granules, specific granules and azurophil granules. Azurophil granules include ionic granule proteins such as "lysosomal enzymes" and defensins. Defensins are antimicrobial peptides capable of inserting themselves into microbial cell membranes via electrostatic interactions [7] or through transmembrane potential driven insertions [8]. The membrane insertion brings about a change in the permeability of the membrane, and ultimately results in demise of the microbe. Defensins are effective against a wide array of organisms including bacteria, fungi and even viruses [9]. These anti-microbial peptides further add to the immune response by scrupulously inducing the migration of CD4+/CD45RA and CD8+ T-cells in humans and also serve as a chemo tactic for immature dendritic cells derived from either peripheral blood monocytes or CD34+ progenitors [10].

Neutrophils also have the ability to produce toxic oxygen species that include hydrogen peroxide, hydroxyl radicals and superoxide anions. These reactive oxygen species (ROS) have numerous functions, including acting as cellular messengers [11], regulating the apoptotic process of neutrophils [12] and modulating other reactive immune cells [13]. The microbicidal role of oxygen derived free radicals are emphasized by their ability to promote lipid peroxidation, DNA damage and the oxidation of proteins, resulting in cell death [14].

Even though neutrophils are the chief motive of the innate immune system, in humans they only spend an average of 5 and half days in circulation [15]. The brief lifespan of neutrophils compared to other innate immune cells, could be attributed to their arsenal of anti-microbial compounds that could induce severe immunopathology and cause serious harm to the host if released unrestrained. Constitutive apoptosis is another mechanism used to control neutrophil numbers, to regulate the inflammatory potential of these innate cells [16]. This essential process maintains the delicate balance between neutrophils behaving as effectors during host defence and neutrophils functioning as inducers of immunopathology. Abadie and colleagues [17] infected mice with a genetically modified strain of *Mycobacterium bovis* bacilli Calmette-Guerin (BCG) that express an enhanced green fluorescent protein (EGFP). Co-expression of EGFP enabled them to determine the essential role neutrophils play in the capture and transport of rBCG-egfp to the secondary lymphoid organs, including Peyer's patches, lymph nodes and spleen. Their results showed that neutrophils can also play a part in antigen presentation *in vivo*. The conclusion was that neutrophils have the capacity to exit the site of infection via the afferent lymphatic system, migrate to the secondary lymphoid tissue and take part in the transport and presentation of live microbes [17].

The release of cytokines and chemokines recruit neutrophils to the site of infection. After an encounter and subsequent infection by *M. tb*, macrophages produce interleukin-8 (CXCL8 or IL-8) [18]. With regards to neutrophil immunity, CXCL8 is one of the most influential chemokines [19]. Neutrophils possess a high number of chemokine receptors that are specific for CXCL8. It serves as a chemo attractant and potent angiogenic factor, crucial for activation and recruitment of neutrophils [19]. A significant correlation exists between the amount of CXCL8 protein present and the number of neutrophils accounted for [20]. Activated human CD4+ T-cells secrete interleukin-17 (IL-17). The cytokine, IL-17 is responsible for inducing an elevated concentration and an increased release of CXCL8 from human bronchial epithelial and venous endothelial cells. It was further illustrated that in vivo, after intra-tracheal addition of hIL-17 (human interleukin-17), neutrophils were selectively recruited to the airways of the rats. Laan et al. [21] established that there exists a link between neutrophil recruitment and T-lymphocytes by demonstrating that hIL-17 mobilizes neutrophils to the site of infection via the release of CXC chemokines [21].

The immune response to intracellular pathogens- a neutrophil's perspective

During infection neutrophils move to the area of infection where they attempt to kill the intruding micro-organism by phagocytosis followed by exposure to ROS and other anti-microbial metabolites. The measure of resistance that the host

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will have against various bacterial and fungal infections is also determined by neutrophils. Elevated chemotaxis accompanied by an increased accumulation of neutrophils in the granuloma suggests another role of these innate cells during *M. tb* infection. By activating DC's (dendritic cells), neutrophils also act as a messenger between the innate and specific acquired immune system [22]. Neutrophils have also shown to enhance immunity. When apoptotic neutrophils, infected with mycobacteria, are phagocytosed by macrophages, the acquired neutrophil granules add to the increased microbicidal effect that these macrophages have against the bacteria [19,21]. After inhalation of *M. tb*, neutrophils and macrophages are of the first cells that come into contact with the bacteria. Macrophages, being a substantial source of CXCL8, are responsible for the increased recruitment of neutrophils to the site of infection. As a result, the newly recruited neutrophils produce cytokines like TNF-α (tumour necrosis factor-alpha) which have a paracrine effect on macrophages [19]. This illustrates that the immune system is interlinked in function, and how various components influence one another to shape the type of immune response that is elicited [23].

Because of their notorious association with immunopathology recognized during acute infection, most data pertaining to neutrophils aim attention at the intracellular killing mechanism and overlook their probable extracellular activities. In recent years [24], described an extracellular, neutrophil-mediated anti-microbial mechanism to contain and kill micro-organisms. This mechanism involves the formation of neutrophil extracellular traps (NETs), as shown in Figure 1, which consist of chromatin, lined with anti-microbial proteins. These proteins are granular in nature and have the ability to contain and kilo gram-positive bacteria [25,26], gram negative bacteria [27] and even fungi [28]. NADPH oxidase, coupled with NET formation, produce ROS responsible for induction of a cell death process unique from necrosis or apoptosis.

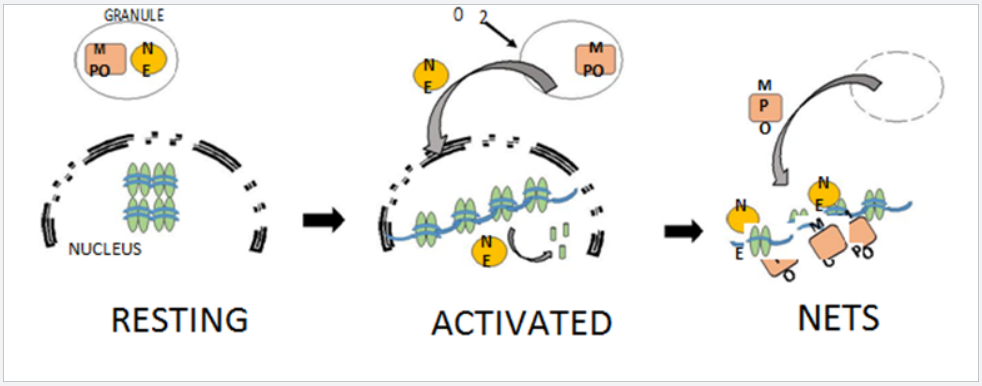

Figure 1: An example of the formation of the neutrophil extracellular trap (NET). The resting neutrophils contain azurophilic granules with neutrophil elastase (NE) and Myeloperoxidase (MPO). Activated neutrophils produce ROS, NE leaks from the granule and moves to the nucleus where it slices histones and aids chromatin decondensation. NE and MPO boost chromatin decondensation and results in the rupture of the cell to release the NET. Adapted from [78].

Phagocytosis, cellular cross-talk and the induction of the adaptive immunity

Neutrophils remain dormant in circulation until they encounter an infectious agent, this is followed by a phase of activation that promotes and enhances inflammatory responses and anti-microbial action [29]. This phase of activation includes various stages of phenotypical and functional changes in neutrophils. The cell surface receptors employed by neutrophils in the interaction with microbes are altered by low levels of activating agents. Direct recognition, as well as opsonisation, the process by which opsonins coat infecting bacteria making them more prone to be phagocytosed, seems to play a key role in the process of mycobacterial internalization. Alemán and colleagues [30] showed that mice deficient in Toll like receptor 2 (TLR2) had reduced control over both *M. avium* and *M. tb* infections, highlighting a role for TLR2. Toll-like receptor 4 (TLR4) should not be neglected, as Godaly [31] illustrated that when TRL4 was blocked, CXCL8 production in response to BCG infection was significantly reduced. Bacteria are phagocytosed once recognition has taken place. Neutrophils play a central role in phagocytosis, the primary mechanism by which pathogens and cell debris are removed from the body. Phagocytosis is a dynamic process mediated by cell receptors. The internalization of microbes occurs through the cell membrane into vacuoles called phagosomes. Inside these vacuoles, microbes are exposed to various anti-microbial peptides and degradative molecules. The type of interaction between the microbe and the neutrophil determine the specific mechanism of internalization that is utilized. As soon as neutrophils exit the circulatory system and enter the site of infection, they interact with invading pathogens and become activated. They are able to partake in specific anti-microbial actions upon stimulation by certain chemokines and cytokines.

With their rapid action against infection, it is evident that neutrophils play an essential part in creating the optimal environment for the host to reciprocate with a suitable adaptive

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immune response. This is accomplished by using chemokines and cytokines as mediators to issue instructions to virtually all other types of immune cells. This is a critical process for the development of an appropriate inflammatory response. Neutrophils maintain a low transcriptional signature during their inactive state in the circulatory blood and only once they encounter infection do they experience an immense transcriptional burst and successive activation which results in the formation of signaling compounds [32,33].

Even though, compared to other immune cells, neutrophils do not produce a large amount of cytokines per cell, at the site of infection or inflammation they are plentiful and present in large numbers, making their relative contribution rather significant [34]. Since the primary response of these innate cells is to boost their numbers, CXCL8 is most abundantly produced due to its main function being to recruit more neutrophils [35]. In addition to chemokines and cytokines, a variety of other signaling compounds are secreted by neutrophils. These include granule content [36], lipids [37], hydrogen peroxide (ROS) and some mediators by means of cell to cell contact [38]. Other leukocytes, such as macrophages, cooperate with neutrophils to combat various pathogenic infections. Using immunohistochemistry, Ramos-Kichik et al. [24] noticed that following a mycobacterial infection, macrophages contained granulocytes. This adequately illustrated that through phagocytosis, macrophages obtained lactoferin, a protein produced by granulocytes such as neutrophils and inherently not present in macrophages. Previously, the presence of neutrophils during mycobacterial infections was thought of as inconsequential and temporary, however, these findings significantly highlighted the function of these leukocytes [23]. Dendritic cells (DCs), classified as probably the most important antigen-presenting cells, have the capacity to capture and present antigens in the secondary lymphoid tissue. They also release interleukin-12 (IL-12) which has been demonstrated to be integral in the stimulation of a T helper 1 (Th1) directed cytokine response [39]. Van Gisbergen et al. [38] confirmed that active neutrophils, both *in vitro* and *in vivo*, robustly cluster with and activate the maturation of DCs. This facilitates them to set off a strong T-cell response directed at a type 1 T-cell polarization. This DC-neutrophil interaction is aided by the binding of C-type lectin unique to DCs (DC-SIGN), to Mac-1 [38]. The interaction of immature DCs with neutrophils may, in distant lymph nodes, modulates immune responses. Bennouna et al. [40] confirmed this with data from a murine study, showing that both DC maturation and cytokine production was induced by neutrophil derived TNF-α. Neutrophils have also been shown to, *in vitro*, collaborate with natural killer (NK) cells and DCs. The study by Costantini et al. [41] f confirmed that neutrophils, using CD18-ICAM-1 interactions, very specifically communicate with DCs. This correspondence promotes the production of IL-12p70 by DCs, which in turn, results in the stimulation of Interferon-γ (INF-γ) production by NK cells and eventually furthers the activation of neutrophils, culminating in a positive feedback loop. Simultaneously, by direct binding (in a cell to cell manner), NK cells become further activated by neutrophils [41].

Neutrophil-associated Chemokines and cytokines

By means of cytokine and pattern-recognition receptors, neutrophils may be directly activated to secrete immuno-modulatory elements [42]. Surprisingly, even cathelicidins and defensins (anti-microbial peptides found inside the granules of neutrophils) have the capacity to be immune-modulatory. Table 1 outlines the function of some of this immune response modulating cytokines.

Table 1: Cytokines and chemokines released by neutrophils during a host immune response, their regular function and the role they play during *M.tb* infection.

Cytokine/chemokine name	Function	Role during Tuberculosis infection
Interleukin-1 (IL-1)	Actively induces fever. It is also responsible for the development of inflammation [43], [44].	Because the signaling of IL-1 is a crucial factor of the MyD88-dependent innate immune response to *M. tb*, it is paramount in the successful resistance, *in vivo*, against *M. tb* infection. The MyD88-dependent response occurs via a caspase-1 independent mechanism [45].
Interleukin-6 (IL-6)	Is versatile with a plethora of activities. Its functions include the terminal maturation of B-cells, the promotion of B-cell antibody production and acting as a growth stimulating molecule on hematopoietic progenitors in conjunction with IL-1 and IL-3 [46].	IL-6 is vital for the activation of macrophages and the generation of pro-inflammatory responses. *M. tb* inhibits the production of IL-6 by means of a stress response factor Sigh. This suggests that IL-6 plays an essential part in the acquired immunity against *M. tb*. IL-6 is fundamental in the generation of a protective Th1 immune response against *M. tb* after vaccination with a subunit vaccine.

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Interleukin-8 (IL-8 / CXCL8)	Induces chemotaxis (by means of a feedback loop, more neutrophils get recruited to the site of infection), respiratory burst and exocytosis. Additionally, CXCL8 up regulates complement receptors 1 and 3 [47]. Interleukin-1 receptor antagonist [48]-proving to play a regulatory part during inflammation by inhibiting (both in vitro and *in vivo*) effects of IL-1 [49].	Lung epithelial cells release IL-8 after stimulation by *M. tb*. Neutrophil recruitment to the site of infection is increased when IL-8 levels are elevated. Even though this enhanced trafficking of neutrophils might be involved in the clearance of *M. tb*, tissue damage may result due to released proteases and oxidants when neutrophils are present in excess.
Tumour necrosis factor-α(TNF-α)	Shows a wide spectrum of effects. It inaugurates fever [50], changes the production of collagenase and prostaglandin E2 by fibroblasts [51], stimulates the synthesis of prostaglandin E2 and IL-1 in resting macrophages [52],initiates osteoclastic bone resorption [53], has the capacity to inhibit lipoprotein lipase [54] and to function cooperatively with other cytokines including IL-1 [55].	The methodical induction of macrophage apoptosis after bacillary infection is a mechanism by which TNF-α is believed to mediate a successful host immune response to mycobacteria. Macrophage apoptosis is an important component of granulomas associated with tuberculosis and might assist in maintaining their integrity
Macrophage inflammatory protein (MIP)-1α/β	An inducible protein partaking in various pro-inflammatory activities. Subsets of leukocytes, such as neutrophils, can be recruited to the site of inflammation by monocyte chemo attractant protein (MCP)-1 [49].	Because of the chemo attractant property of macrophage inflammatory proteins, they are likely to play a considerable part in respiratory tract defences during infections such as tuberculosis [56].
Growth regulated alpha protein (GRO-α)	An inducible protein partaking in various pro-inflammatory activities. Subsets of leukocytes, such as neutrophils, can be recruited to the site of inflammation by monocyte chemo attractant protein (MCP)-1 [49]. Is produced in guinea pigs, mice and humans [57], [58], [59] and believed to be a member of the pro-inflammatory group of cytokines. It also contributes to the inhibition of apoptosis.	The chemokines secreted by neutrophils may play an essential part in the development and advancement of *M. tb* inflammation. It has been validated, *in vitro* and *in vivo*, that neutrophils produce cytokines in response to *M. avium, M. bovis* BCG and *M. tb* stimulation [58], [60].

Neutrophils activating B-cells : a special focos on the study by Puga et al. [4]

Collaboration between the innate and adaptive arms of the immune system is required for the successful eradication of pathogens. While the innate branch launches a rapid, less specified response against pathogens by recognizing conserved microbial patterns, the adaptive response is highly specific and somewhat delayed, taking days to become apparent. The participation of innate immune cells in the mediation of B-cell responses has been generally restricted to opsonisation and phagocytosis of pathogens coated with antigens. However, studies by Chen et al. [61] and Chu et al. [62] illustrated that innate immune cells, basophils and eosinophils respectively, secrete factors such as interleukin-6 (IL-6), a proliferation-inducing ligand (APRIL), B-cell-activating factor of the TNF family (BAFF), which stimulate the activation of B-cells. Similarly, it has been shown that neutrophils impact adaptive immune responses during infection by regulating the activation of dendritic cells by way of interleukin-10 [63] and alarmins [36]. However, it has been largely unknown how neutrophils regulate a response in the humoral branch of the adaptive immune system. In a pioneering study by Andrea Cerutti, the authors demonstrated that splenic neutrophils have the capacity to act as proficient helper cells for splenic marginal zone (MZ) B-cells, resulting in the generation of matured antibodies with increased affinity for a specific antigen (fully illustrated in Figure 2. The study commenced by analyzing neutrophil distribution in tissue sections taken from peripheral lymphoid organs of individuals free from infection or inflammation. They observed in regions neighboring the splenic MZ that neutrophils were found in abundance. The aforementioned distribution is observed in both mice and macaques, which implied that these neutrophils around the MZ might be consequential in the maintenance of homeostasis. Moreover, in pathological spleens this distribution changes, such that neutrophils penetrate the germinal centres and follicular mantle. The confinement of neutrophils to the area around the MZ signifies that they are in an optimal location to react to circulating antigens and also leave them in adjacent to MZ B-cells. These B-cells are usually linked with antibody responses that are T-cell independent. In light of this, the authors showed that splenic neutrophils differ from those in circulation in such that in MZ B-cells they are able to moderate activation

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of IgM secretion. Subsequently these cells were termed B-helper neutrophils (NBH), and an in depth analysis of this population unveiled the possible molecular mechanism by which they regulate MZ B-cell activation. Compared to general circulating neutrophils, expression of B-cell stimulating molecules such as APRIL, BAFF, Interleukin-21 and CD40L, are significantly up regulated in NBH. Furthermore, activation of MZ B-cells can occur in medium conditioned with NBH cells, an effect that is annulled when signaling is blocked through these receptors. However, activation of MZ B-cells seems to be influenced by contact–dependent mechanisms as well since greater antibody secretion is observed after incubation with NBH cells. Interestingly, unlike general circulating neutrophils, the NBH community impulsively forms neutrophil extracellular trap (NET) like projections containing DNA. Lead better and colleagues [64] proposed that NETs might serve as a potential source of toll-like receptor 9 ligand containing immune complexes, which might facilitate activation of B-cells. Nevertheless, the identification of a NBH cell population (able to acts as proficient helper cells for specifically MZ B-cells) unveils an intriguing new avenue for the correspondence between the adaptive and innate immune branches.

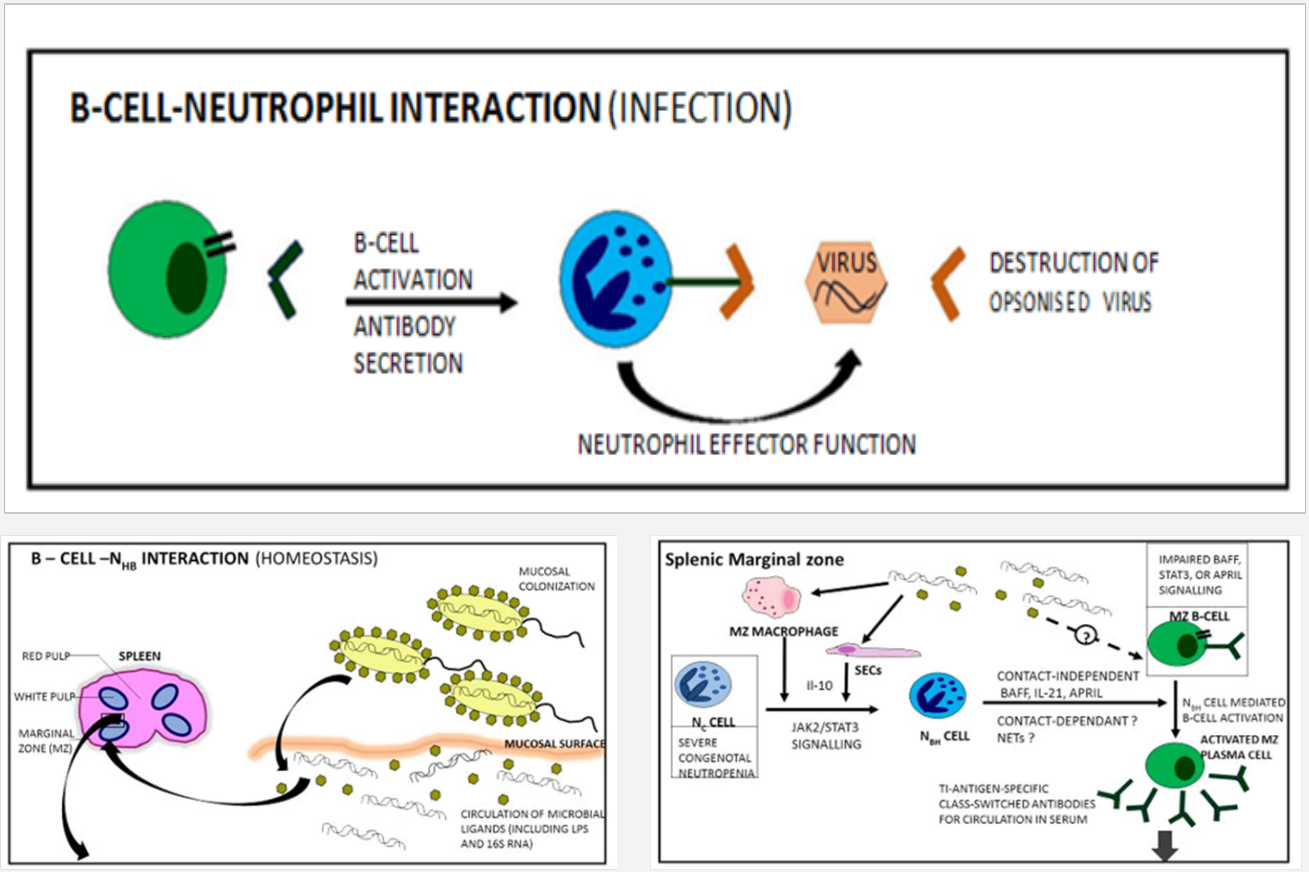

Figure 2: Interaction between B cells and neutrophils. (A) Upon infection, B cells (green) secrete antibodies that coat microbes. Neutrophils (blue) opsonise these coated pathogens. (B) Splenic marginal zone (MZ, pink) B cells (green) are activated to secrete antibodies by the newly identified B-helper neutrophil subset (NBH, dark blue) against T-cell-independent antigens. This activation is mediated by the secretion of IL-21, BAFF and APRIL in a contact-independent mechanism. Neutrophil extracellular traps (NETs) and contact-dependant mechanisms might also play a part. Circulatory neutrophils (Nc) give rise to NBH. This occurs through JAK2 and STAT3 signaling in response to IL-10 secretion by sinusoidal endothelial cells (SECs) and/or macrophages. Adapted from [64].

How is the MZ B-cell population affected by this NBH-mediated support? The activation of follicular B-cells following T-cell dependent antigen presentation is generally partnered with the development of germinal centre's, this has been adequately described [65]. Germinal centre's have commonly been associated with the process of somatic hyper mutation (SHM) which generates a plethora of Ig genes and results in an assemblage of high-affinity clones as well as the development of immunological memory. Nonetheless, even though it has been shown that during a systemic infection, CD11c(lo) dendritic cells encourage the development of IgM-secreting plasma blasts from MZ B-cells [49], considerably less is known about the influence of helper cell assistance on the initiation of T-cell independent immune responses. This study by Puga et al. [4] demonstrated that the expression of transcription factors such as XBP1 and Blimp1 as well as surface marker CD38 in MZ B-cells, is triggered by NBH cells. The expression of these factors is an indication of the formation of plasma blasts. Moreover, as expression of AID (a

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DNA-editing enzyme necessary for class-switch recombination and somatic hyper mutation) is up regulated in MZ B-cells in the vicinity of NBH cells, class switching was shown to have occurred in secreted antibodies, with generation of IgA and IgG2 being favored. Notably, even though in individuals with severe congenital neutropenia (abnormally low neutrophil count), levels of class-switched antibodies in response to T-cell dependent antigens were normal. Decreased levels of IgG and IgA in response to T-cell independent antigens, like lipopolysaccharides (LPS) were observed. Sequencing indicated that, at least in humans, NBH-activated MZ B-cell secreted antibodies acquire mutations similar to those observed during somatic hypermutation. Interestingly, the assistance from NBH-cells seem to trigger antibody expansion from MZ B-cells, this effect is similar to that of CD4+ T-cells on follicular B-cells. The origin of these NBH cells comes into question, given their ability to mediate class-switched antibody secretion from MZ B-cells. When general circulating neutrophils are exposed to interleukin-10, they become inducible NBH-like cells and expression of APRIL and BAFF is up regulated. STAT3 and JAK2 signaling is required for the generation of this inducible population. Sinusoidal epithelial cells, in response to microbial peptides, secrete a variety of neutrophil-attracting chemokines as well as interleukin-10. These sinusoidal epithelial cells are found close to NBH cells in the splenic MZ. In light of this, Puga et al. [4] postulated that microbial ligands, entering the circulation by translocation across microbial surfaces [66], prompt both chemotactic signals to and reprogramming of circulating neutrophils which result in the generation of a NBH population. In agreement with this, splenic NBH cells are established early in fetal life, but only about two days after birth is this population significantly enhanced, this event coincides with the bacterial colonization of mucosal surfaces. Furthermore, mice that are either unable to generate toll-like receptor signaling or are born germ free, have a decreased NBH population. These observations suggest that given a healthy and functional immune system, NBH cells stimulate the formation of class-switched antibodies from MZ B-cells in response to T-cell independent microbial antigens under steady state conditions.

The neutrophil response to tuberculosis infection

Various studies show definitive evidence that neutrophils are essential to the protective immune response against *M.tb* infection [17,57,67]. Martineau and colleagues [68] provided evidence that neutropenia led to a considerable decline in both BCG and *M. tb* levels in whole blood. Numerous studies adequately showed that neutrophils play a major role in the immunopathology during pulmonary tuberculosis infection, with some stating that they are noxious to the host's control of the mycobacterial infection [54-56]. Another study showed that following intratracheal infection, a TB susceptible mouse strain had surprisingly high levels of neutrophils accumulating in the lungs for extended periods [69]. In comparison to less susceptible strains, they demonstrated prolonged existence and lower expression of the CD95 apoptotic receptor associated with greater mobility and phagocytic proficiency of *M. tb*. The study concluded that the development of immunopathology during tuberculosis infection was driven by the above mentioned features as well as the fact that/ compared to macrophages, neutrophils battle to control mycobacterial growth [70]. In recent years it became apparent that neutrophils are the main cells infected with actively replicating mycobacteria [71]. This adds to the intricacy of the part they play in *M.tb* infection, indicating that they act as a concealed stratagem during host infection with *M. tb*.

Neutrophils have a broad spectrum of anti-microbial actions. One such action involves the use of human neutrophil peptides (HNPs) which form part of the defensin family of anti-microbial proteins [72]. Mice infected with *M. tb* H37Rv have shown a significant reduction in the bacillary load in liver spleen and lungs after time and dose dependent treatment with HNP-1 [73]. Martineau et al. [53] also illustrated that HNPs 1-3 kill *M. tb* in microbiological media. Neutrophils produce lipocalin 2 and cathelicidin LL-37, these peptides both have the ability to restrict mycobacterial growth, with lipocalin 2 acting in an iron dependent manner [74]. This evidence indicates that neutrophils play a considerable part in the host defence during innate immunity. Antimicrobial peptide production facilitates this defense.

During inflammation neutrophils actively produce and secrete a serine proteinase known as ELA2 or leukocyte elastase. It forms part of the chymotrypsin family and has significant microbicidal activity by killing target bacteria and destroying host tissue [75]. ELA2 comprises of three amino acid residues; histidine, aspartate and serine, which are involved in a charge, relay system. This charge relay system allows for the proteinase activity. Within the primary polypeptide these residues are dispersed throughout, it is only once the protein has folded and its three dimensional conformation is complete, that these residues form a triad capable of proteinase activity [76]. Azurophil granules contain ELA2. The function of this elastase is to hydrolyse wide variety of proteins inside the azurophil granules as well as proteins in the extracellular matrix, following its release from the azurophil granules. Neutrophil elastase kills gram-negative bacteria [77], facilitates NET production [78] and degrades bacterial virulence factors [77]. When activated, neutrophil elastase translocates to the nucleus where it partially digests certain histones, promoting chromatin decondensation and leading to NET formation [79]. Myeloperoxidase (MPO), in the presence of ROS such as hydrogen peroxide, had persistent microbicidal action against *M.tb* H37Rv [79]. When activated, granulocytes such as neutrophils, utilize the myeloperoxidase-H2O2-Cl- system to generate reactive aldehydes [80] which at the site of inflammation, covalently alter both membranous and soluble proteins of cells [81]. Also, MPO acts in conjunction with neutrophil elastase to independently drive chromatin decondensation from the elastase's enzymatic activity [78].

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Lactoferrin, a multifunctional immune protein present in a range of secretory fluids is also contained within the secondary granules of polymorphonuclear leukocytes such as neutrophils [82]. A further study [83] demonstrated the antibacterial capabilities of human lactoferrin early on. This is achieved by lactoferrin sequestering iron from the environment, making this vital element unattainable to potential pathogens [84]. Lactoferrin functions as an adjunct adjuvant in BCG vaccine efficacy and this leads to a boost in protection against future trials with virulent M. tb. An increase in the production of IL-12(p40) as well as an increase in relative ratios of IL-12/IL-10 was observed in mice after a single immunization with lactoferrin [84], this would, in turn, result in the increased recruitment and production of neutrophils.

Neutrophils extracellular traps (NETs) also demonstrate a unique mechanism for the control of infections with intracellular mycobacteria. The formation of NETs is brought about by cellular changes induced by *M. tb*, resulting in neutrophil death and subsequent release of *M. tb* [24]. Even though NETs are able to capture mycobacteria after their release, they are not able to eradicate them. *In vivo* mycobacterial control could be facilitated by the trapping of *M. tb* by NETs thus restricting distribution of mycobacteria and limiting the infection to the local environment only. A different function for the NET-mediated trapping of *M .tb* is presumably the sequestering of local chemokines and cytokines, thus initiating granuloma development by promoting recruitment of other phagocytes. Since only a proportion of neutrophils undergo NET formation, the remaining neutrophils are believed to play a role in phagocytosis and other neutrophilic obligations [24]. Even though reactive oxygen species are produced, the combined action with NETs does not eradicate mycobacteria as successful as other microbes [24,85]. It is suggested that NETs bind to the electron dense layer on the outermost structure of mycobacteria. This structure is composed of polysaccharides with their negatively charged groups exposed [86,87].

Neutrophils are capable of undergoing apoptosis [12,13,58]. After phagocytosis by neutrophils, mycobacteria are exposed to a variety of antibacterial substances within the intracellular environment of the neutrophil. If these bactericidal substances fail to successfully eradicate the microbe, the neutrophil induces apoptosis in a final effort to eliminate the phagocytosed bacteria. It has also been proposed that in an attempt to be spared from the immune response, mycobacteria induce apoptosis in neutrophils after infection [88-91].

TNF-α is one cytokine responsible for inducing apoptosis in neutrophils [92]. This was illustrated in vitro [93] that neutrophils stimulated with TNF-α and bacterial lipopolysaccharide (LPS) resulted in apoptosis. The study also suggested that apoptosis might be the cause for the low viability observed with neutrophils, and that the obliteration of these neutrophils, unsuccessful in their attempt to kill the mycobacteria, tips the scale towards the infiltration of mononuclear cells rather than neutrophils, during the alteration of the inflammatory immune response against M. tb infection. They also proposed that the rapid cell death of neutrophils at the site of infection might be attributed to *M. tb* [94].

Concluding Remarks

Neutrophils are traditionally convicted of being destructive, they arrive on the scene too early, in colossal numbers, and their reaction is unmerciful and usually leads to immunopathology. As more discoveries are made regarding these innate immune cells, however, neutrophils are beginning to emerge as influential mediators between innate and adaptive immune branches and crucial for an effective immune response against pathogens. They function as effectors with a plethora of cytotoxic constituents at their disposal, as well as preparing the micro environment for the more specific adaptive response by secreting the required chemokines and cytokines. They instruct monocytes, dendritic cells and other lymphocytes and serve as a direct connection between innate and humoral immune responses. They greatly influence the decision to initiate, alter or maintain a specific immune response. Being the devoted front line fighters that they are, they fight in life and even in death and come prepared with an arsenal of weaponry against pathogens such as *M. tb*, employ kamikaze tactics by apoptosis and form NETs through specialized cell death.

Future Research on the Role of Neutrophils

Uncovering the full complexity of the mechanism by which neutrophils operate proves to remain a challenge. Unanswered questions that still remain include:

A. The source of the initial signal that initiates formation of the NBH population and

B. The specific regulatory mechanism by which NBH-mediated MZ B-cells are activated. Answers to these questions could lead to potential therapeutic advances in the enhancement of basal immunity by the calculated manipulation of neutrophils.

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